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     (FILE 'HOME' ENTERED AT 09:52:05 ON 27 JAN 2003)

     FILE 'CAPLUS, MEDLINE' ENTERED AT 09:52:17 ON 27 JAN 2003
L1         20205 S PHOSPHODIESTERASE (L) (5 OR V) OR PDE5
L2         36130 S PE OR PREMATURE EJACULATION
L3       1365760 S SECONDARY OR PRIMARY
L4          1726 S L2 AND L3
L5             4 S L4 AND L4 AND L1
L6             3 DUP REM L5 (1 DUPLICATE REMOVED)
L7            15 S EJACULATION AND L1
L8             0 S L7 AND L3
L9            12 DUP REM L7 (3 DUPLICATES REMOVED)
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ACCESSION NUMBER: 97016308 MEDLINE
DOCUMENT NUMBER: 97016308 PubMed ID: 8862943
TITLE: The aetiology and management of erectile, ejaculatory, and fertility problems in men with diabetes mellitus.
AUTHOR: Dunsmuir W D; Holmes S A
CORPORATE SOURCE: Department of Urology, St George's Hospital, London, UK.
SOURCE: DIABETIC MEDICINE, (1996 Aug) 13 (8) 700-8. Ref: 96
Journal code: 8500858. ISSN: 0742-3071.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970113
AB Erectile impotence is more common in the diabetic than the general population, occurs at a younger age, and is often associated with ejaculatory problems. For these, and possibly for other more subtle reasons, fertility may be a problem for men with diabetes. The symptoms of erectile and ejaculatory dysfunction are frequently not discussed between patient and doctor. Psychological factors are important but the vast majority of diabetic patients have an organic basis for their impotence. Both neurogenic and vascular factors are important in the pathogenesis of erectile failure. Autonomic neuropathy is almost certainly the cause of the ejaculatory failure that may be present in up to 40% of men with diabetes. The final biochemical mediator of erection within the penile erectile tissue is nitric oxide and a key enzyme in its degradation is **phosphodiesterase** (type **V**). Drugs that affect the metabolism of this enzyme are being developed to treat erectile failure. At present, the self injection of intra-cavernosal erectogenic agents (such as prostaglandin E1) provide the main form of therapy for erectile failure. Vacuum devices are a simple alternative and venous ligation surgery may be effective for a properly selected cohort of patients. Prosthetic implants are a final option for patients in whom all else has failed. Fertility problems, particularly when associated with ejaculatory failure can be overcome with modern assisted reproductive techniques. Nowadays, these will frequently involve gamete micro-manipulation.

L9 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
ACCESSION NUMBER: 2000:97156 CAPLUS
DOCUMENT NUMBER: 133:12709
TITLE: Effects of sildenafil (Viagra) administration on seminal parameters and post-ejaculatory refractory time in normal males
AUTHOR(S): Aversa, Antonio; Mazzilli, Fernando; Rossi, Tiziana; Delfino, Michele; Isidori, Andrea M.; Fabbri, Andrea
CORPORATE SOURCE: Cattedra di Andrologia, University of Rome La Sapienza, Rome, Italy
SOURCE: Human Reproduction (2000), 15(1), 131-134
CODEN: HUREEE; ISSN: 0268-1161
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sildenafil is a specific inhibitor of **phosphodiesterase** (PDE) type **5** and represents a powerful therapy for male erectile dysfunction (ED) of different etiol. Recently, sildenafil has been shown to restore erections in temporary ED related to the need of semen collection for assisted reproductive techniques. In this study, we investigated whether sildenafil administration modifies seminal parameters and/or erectile function in normal healthy volunteers. In a double-blind, randomized, placebo-controlled, cross-over two period investigation we enrolled 20 healthy male volunteers (mean .+-. SE age 32.+-.0.**5** yr). Subjects were not using any medication for the 3 mo period prior to the study and were engaged in a stable relation with proven fertility. The effects of sildenafil (100 mg) on seminal parameters and erectile function after audiovisual sexual stimulation were evaluated by semen anal. and by color-Duplex ultrasound (the Resistive Index) resp. In all subjects, sildenafil caused no changes in seminal and erection parameters when compared to placebo. Interestingly, sildenafil administration led to a marked redn. of the post-ejaculatory refractory time (10.8.+-.0.9 min vs. 2.6.+-.0.7 min for placebo and sildenafil resp.; $P < 0.0001$). These results indicate that in normal subjects acute sildenafil treatment does not modify semen characteristics and has a pos. influence over the resumption of erections following **ejaculation** in the presence of a continuous erotic stimulus.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 12 MEDLINE
ACCESSION NUMBER: 2001286250 MEDLINE
DOCUMENT NUMBER: 21148958 PubMed ID: 11253255
TITLE: Sexual pharmacology in the 21st century.
AUTHOR: Rosen R C
CORPORATE SOURCE: Department of Psychiatry, Center for Sexual and Marital Health, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA.
SOURCE: J Gend Specif Med, (2000 Jul-Aug) 3 (5) 45-52.
Journal code: 100887298. ISSN: 1523-7036.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered Medline: 20010524
AB Sexual dysfunction is highly prevalent in both sexes. Considerable progress has been made in the development of new pharmacologic treatments since the approval of sildenafil in 1998. A variety of oral erectogenic

agents are available or are in late-phase development, including centrally active dopamine agonists (e.g., sublingual apomorphine), peripheral nonselective alpha-blockers (e.g., oral phentolamine), and other **phosphodiesterase** type-**5** inhibitors (e.g., vardenafil). These drugs have recently been evaluated for the treatment of female sexual arousal disorder, although results to date have been inconclusive. Pharmacologic therapies have also been proposed for the treatment of premature **ejaculation** and hypoactive sexual desire disorder. Strong evidence exists for the value of serotonergic drugs (e.g., selective serotonin reuptake inhibitors) in the treatment of premature **ejaculation**. Further research is needed, particularly on the effects of these drugs on female sexual dysfunction.

L9 ANSWER 9 OF 12 MEDLINE
ACCESSION NUMBER: 1999352442 MEDLINE
DOCUMENT NUMBER: 99352442 PubMed ID: 10421800
TITLE: Detection of mRNA transcripts of cyclic nucleotide phosphodiesterase subtypes in ejaculated human spermatozoa.
AUTHOR: Richter W; Dettmer D; Glander H
CORPORATE SOURCE: Department of Biochemistry, and Department of Dermatology, Andrological Unit, University of Leipzig, Liebigstrasse 21, D-04103 Leipzig, Germany.
SOURCE: MOLECULAR HUMAN REPRODUCTION, (1999 Aug) 5 (8) 732-6. Journal code: 9513710. ISSN: 1360-9947.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991004

AB Multiple types and subtypes, including splice variants, of cyclic nucleotide **phosphodiesterases** (PDE) have been shown to be expressed in various tissues and organs. They control the intracellular level of cyclic nucleotides and are involved in hormonal signalling. In human spermatozoa, PDE play an important role in the regulation of motility, capacitation and acrosome reaction. The aim of this study was to investigate which transcripts of the different PDE types and subtypes could be found in human spermatozoa using reverse transcription-polymerase chain reaction (RT-PCR). Ejaculated spermatozoa from 10 single semen samples as well as another three semen sample pools were separated by swim-up and were investigated by RT-PCR. We obtained PCR products of the PDE types/subtypes 1A/B/C, 2, 3A/B, 4A/B/C, **5**, and 8 with different intensities. Control PCR for leukocyte contamination were negative and contamination by other somatic cells was excluded by the spermatozoa preparation protocol, immunohistochemistry and visual examination. These results demonstrated for the first time that human ejaculated spermatozoa contain an extended pattern of PDE mRNA transcripts.

CCESSION NUMBER: 2000:610555 CAPLUS
DOCUMENT NUMBER: 133:168355
TITLE: Compositions comprising bupropion for the treatment of premature **ejaculation**
INVENTOR(S): Grassler, Frank Peter
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: Brit. UK Pat. Appl., 11 pp.
CODEN: BAXXDU
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2340037	A1	20000216	GB 1999-17346	19990726

PRIORITY APPLN. INFO.: US 1998-94701P P 19980730

AB A compn. comprising bupropion or physiol. acceptable salts, solvates, or enantiomers thereof, is used for the treatment of premature **ejaculation** that is either caused by a phys. disorder or that is induced by a cGMP **phosphodiesterase** inhibitor or a cGMP **phosphodiesterase V** inhibitor, such as sildenafil. The compn. may comprise bupropion and sildenafil for the treatment of erectile dysfunction and sildenafil-induced premature **ejaculation**.

L9 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:659569 CAPLUS
DOCUMENT NUMBER: 137:210286
TITLE: Vardenafil
AUTHOR(S): Ormrod, Douglas; Easthope, Stephanie E.; Figgitt, David P.
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs & Aging (2002), 19(3), 217-227
CODEN: DRAGE6; ISSN: 1170-229X
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Vardenafil selectively inhibits **phosphodiesterase** type **5** (**PDE5**), an enzyme which hydrolyzes cyclic guanosine monophosphate in the cavernosum tissue of the penis. Inhibition of **PDE5** results in increased arterial blood flow leading to enlargement of the corpus cavernosum. Because of the increased tumescence, veins are compressed between the corpus cavernosum and the tunica albuginea, resulting in an erection. Vardenafil has a high bioavailability and is rapidly absorbed. An erection of >60% rigidity was maintained for approx. twice as long following visual stimulation in patients treated with vardenafil 10 or 20mg than in recipients of placebo. In a large, placebo-controlled trial in patients with mild to severe erectile dysfunction (ED), vardenafil **5**, 10 or 20mg taken as needed over a 12-wk period significantly improved the scores in questions 3 and 4 of the International Index of Erectile Function (IIEF). The rate of successful attempts at intercourse with **ejaculation** was also significantly higher with vardenafil (71 to 75%) than in the placebo group (39.**5**%), and significantly more patients treated with vardenafil than placebo responded 'yes' to a Global Assessment Question (GAQ) asking if treatment had improved erections. In a 26-wk trial in 736 men with ED of varied etiologies and severity patients receiving vardenafil **5**, 10 or 20mg experienced significantly improved erections with 85% of vardenafil 20mg recipients reporting improved erectile function (assessed using the GAQ) compared with 28% of placebo recipients. Treatment with vardenafil also significantly improved scores in response to questions 3 and 4 of the IIEF compared with placebo. A 12-wk trial in 452 men with ED assocd. with diabetes mellitus demonstrated that treatment with vardenafil 20mg compared with placebo significantly improved IIEF erectile function domain scores and the rate of pos. responders to the erectile improvement GAQ. Similar results were reported in a placebo-controlled trial of vardenafil 10 to 20mg involving 440 patients with ED after radical prostatectomy. Adverse events assocd. with vardenafil were those commonly assocd. with **PDE5** inhibitors: headache, flushing, dyspepsia and rhinitis. These were mostly dose-dependent and mild to moderate in intensity.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:391540 CAPLUS
DOCUMENT NUMBER: 136:380144
TITLE: **Phosphodiesterase V** inhibitors for the treatment of premature **ejaculation**
INVENTOR(S): Boolell, Mitradev
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002040027	A1	20020523	WO 2001-IB2180	20011119
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002091129	A1	20020711	US 2001-990955	20011116
AU 2002015149	A5	20020527	AU 2002-15149	20011119

PRIORITY APPLN. INFO.:
GB 2000-28245 A 20001120
US 2001-260564P P 20010109
WO 2001-IB2180 W 20011119

AB The invention relates to the use of cGMP **phosphodiesterase V** inhibitors, including in particular the compd. sildenafil, for the treatment of premature **ejaculation** in patients with normal erectile function.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:51273 CAPLUS
DOCUMENT NUMBER: 136:96099
TITLE: Treatment of male sexual dysfunction
INVENTOR(S): Naylor, Alasdair Mark; Van der Graaf, Pieter Hadewijn; Wayman, Christopher Peter
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002003995	A2	20020117	WO 2001-IB1187	20010702
WO 2002003995	A3	20020418		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002052370 A1 20020502 US 2001-893585 20010628

PRIORITY APPLN. INFO.: GB 2000-16684 A 20000706
GB 2000-30647 A 20001215
GB 2001-6167 A 20010313
GB 2001-8483 A 20010404
US 2000-219100P P 20000718
GB 2001-1584 A 20010122
US 2001-274957P P 20010312

OTHER SOURCE(S): MARPAT 136:96099

AB The present invention relates to the use of neutral endopeptidase inhibitors (NEPi) and a combination of NEPi and phosphodiesterase type (**PDE5**) inhibitor for the treatment of male sexual dysfunction, in particular MED.

L9 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:833515 CAPLUS
DOCUMENT NUMBER: 137:333176
TITLE: As-needed administration of tricyclic and other non-SRI antidepressant drugs to treat premature **ejaculation**
INVENTOR(S): Tam, Peter; Gesundheit, Neil; Wilson, Leland F.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of U.S. Ser. No. 721,412.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002161016	A1	20021031	US 2001-996407	20011121
US 6495154	B1	20021217	US 2000-721412	20001121

PRIORITY APPLN. INFO.: US 2000-721412 A2 20001121

AB A method is provided for treatment of premature **ejaculation** by administration of an antidepressant drug selected from tricyclic antidepressants, tetracyclic antidepressants, MAO inhibitors, azaspirone antidepressants, and atypical non-SRI antidepressants. In a preferred embodiment, administration is on as "as-needed" basis, i.e., the drug is administered immediately or at most several hours prior to sexual activity. Pharmaceutical formulations and packaged kits are also provided.

L9 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:241329 CAPLUS
DOCUMENT NUMBER: 136:284433
TITLE: Administration of phosphodiesterase inhibitors for the treatment of premature **ejaculation**
INVENTOR(S): Wilson, Leland F.; Doherty, Paul C.; Place, Virgil A.; Smith, William L.; Abdel-Hamid, Abdou Ali Ibrahim Aboubakr
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 467,094.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002037828	A1	20020328	US 2001-888250	20010621
US 6403597	B2	20020611		
US 6037346	A	20000314	US 1998-181070	19981027
WO 2003000343	A2	20030103	WO 2002-US9415	20020325

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 1997-958816	B2	19971028
US 1998-181070	A2	19981027
US 1999-467094	A2	19991210
US 2001-888250	A	20010621

AB A method is provided for treatment of premature **ejaculation** by administration of a **phosphodiesterase** inhibitor, e.g., an inhibitor of a Type III, Type IV, or Type **V** **phosphodiesterase**. In a preferred embodiment, administration is on as "as needed" basis, i.e., the drug is administered immediately or several hours prior to sexual activity. Pharmaceutical formulations and packaged kits are also provided. Zaprinast 1.0, mannitol 1.0, microcryst. cellulose 2.0, and magnesium stearate 10 mg are blended in a suitable mixer and then compressed into sublingual tablets. Each sublingual tablet contains 10 mg zaprinast.

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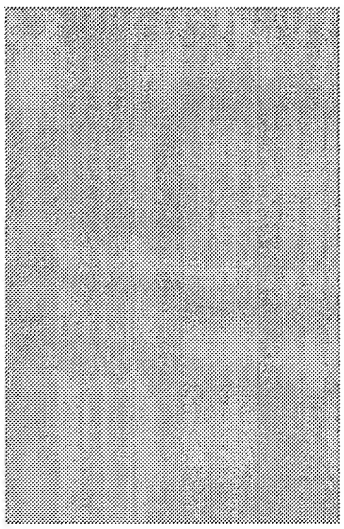

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The Official Journal of the Partnership for Women's Health

Sexual Pharmacology in the 21st Century

Raymond C. Rosen, PhD

Dr. Rosen is from the Department of Psychiatry, Center for Sexual and Marital Health, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ. Address for correspondence: Raymond C. Rosen, PhD, Professor of Psychiatry, UMDNJ-Robert Wood Johnson Medical School, 671 Hoes Ln, Piscataway, NJ 08854.

"The desire to take medicine is perhaps the greatest feature which distinguishes man from animals."

- Sir William Osler

Sexual dysfunction is highly prevalent in both sexes. Considerable progress has been made in the development of new pharmacologic treatments since the approval of sildenafil in 1998. A variety of oral erectogenic agents are available or are in late-phase development, including centrally active dopamine agonists (eg, sublingual apomorphine), peripheral nonselective alpha-blockers (eg, oral phentolamine), and other phosphodiesterase type-5 inhibitors (eg, vardenafil). These drugs have recently been evaluated for the treatment of female sexual arousal disorder,

although results to date have been inconclusive. Pharmacologic therapies have also been proposed for the treatment of premature ejaculation and hypoactive sexual desire disorder. Strong evidence exists for the value of serotonergic drugs (eg, selective serotonin reuptake inhibitors) in the treatment of premature ejaculation. Further research is needed, particularly on the effects of these drugs on female sexual dysfunction.
(The Journal of Gender-Specific Medicine 2000;3[5]:45-52)

Major advances have occurred in our understanding of the basic mechanisms of **sexual** response and the effects of pharmacologic agents on **sexual** desire, arousal, and orgasm. In 1998, the field of **sexual pharmacology** gained enormous impetus from the approval of sildenafil (Viagra), the first oral agent for the treatment of erectile dysfunction (ED).[1,2] A variety of drugs are currently in development for the treatment of ED, and additional pharmacologic agents have been developed for the management of other **sexual** disorders, such as premature ejaculation, hypoactive **sexual** desire, and hyperactive **sexual** desire.

In the early 1990s, studies of the deleterious effects of various classes of prescription and nonprescription drugs, particularly antihypertensives and antidepressant agents, revealed a negative effect on **sexual** function and spurred efforts to counteract these effects.[3,4] These studies indicated that large numbers of male and female patients have **sexual** difficulties due to an underlying medical condition or as an iatrogenic effect of treatment. **Sexual pharmacology** research has also been stimulated by the current interest in quality-of-life outcomes in medical care and the awareness of **sexual** satisfaction as an important component of overall quality of life or satisfaction.

This article will focus primarily on the role of new pharmacologic agents for the treatment of specific **sexual** disorders in men and women. Male erectile dysfunction has been the major area of focus in the past decade. Other specific areas of interest include premature ejaculation, hypoactive **sexual** desire, and **sexual** addiction. Significant advances have been made in pharmacologic treatment in each of these areas. Although less attention has been devoted to the treatment of **sexual** disorders in women, this article will consider some research in the

pharmacologic treatment of female sexual dysfunction. Other papers in this journal have considered the role of hormonal and nonpharmacologic treatments for female disorders.[5,6] More research is clearly needed in this area.

Several factors have contributed to the current focus on pharmacologic therapy for male erectile dysfunction. These include:

1. The relative prevalence of the disorder, particularly in men above the age of 60. According to recent data from the Massachusetts Male Aging Study,[7] 49% of men aged 65 to 69 years of age have moderate to complete erectile dysfunction.

2. The high rate of comorbidity associated with the disorder, including depression, diabetes, hypertension, and other cardiovascular disorders.

3. The availability of a wide range of treatment options, including surgical implants, intracavernosal injections, vacuum erection devices, counseling, and, most recently, oral pharmacologic agents.

4. Major advances in basic research on the pathophysiology of male erectile dysfunction. In particular, understanding of the mechanisms underlying vasodilation and corporal smooth muscle relaxation in the penis have been the subject of intensive investigation in recent years.

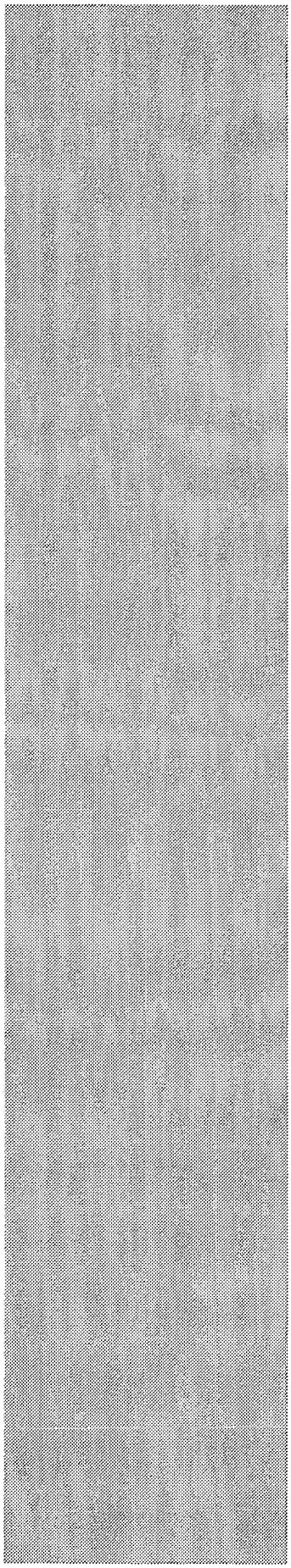
Based on these factors, sexual pharmacology research has focused primarily on the development of new drugs for the treatment of male erectile dysfunction.

Oral Erectogenic Agents

The major classes of drugs currently under development are phosphodiesterase inhibitors (sildenafil), dopamine agonists (apomorphine SL), central alpha-2 antagonists (yohimbine, delequamine), and peripheral alpha-1/alpha-2 blockers (phentolamine).

Phosphodiesterase Type-5 Inhibitors

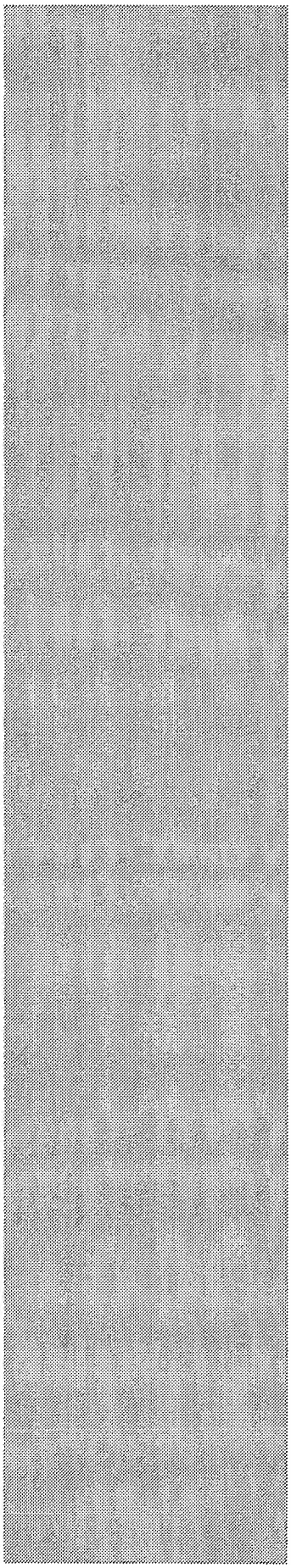
Normal penile erection depends on the relaxation of smooth muscles in the penile corpora.[8,9] In response to sexual stimulation, cavernous nerves and endothelial cells release nitric oxide, which stimulates the formation of



cyclic guanosine monophosphate (GMP) by guanylate cyclase, which in turn causes vasodilation and relaxation of the corporal smooth muscle tissue. Sildenafil citrate is a selective inhibitor of cyclic GMP-specific phosphodiesterase type-5, the predominant isozyme that metabolizes cyclic GMP in the corpus cavernosum. By selectively inhibiting cyclic-GMP catabolism in cavernosal smooth-muscle cells, sildenafil restores the natural erectile response to **sexual** stimulation, but does not cause erection in the absence of **sexual** stimulation. Sildenafil is rapidly absorbed, with maximal plasma concentrations occurring within one hour after oral administration and a mean terminal half-life of three to five hours.

The safety and efficacy of sildenafil have been investigated in many controlled clinical trials in males with erectile dysfunction of varying etiologies. In two large-scale, multicenter trials, sildenafil was administered in doses of 25 mg, 50 mg, and 100 mg, compared to placebo, in either a fixed-dose or flexible-dose regimen.[1] The majority of patients in both studies were judged to have erectile dysfunction of organic etiology (70%), with fewer patients having psychogenic (11%) or mixed (18%) etiologies. Both studies showed significant dose-related improvements for all measures of erectile function and treatment satisfaction with each of the sildenafil doses compared to placebo. In the dose escalation study, 69% of all attempts at **sexual** intercourse were successful for the men receiving sildenafil, compared to 22% for those receiving placebo ($P < .001$). Headache, flushing, and dyspepsia were the most common adverse effects in the dose-escalation study, occurring in 6% to 18% of the men. Other studies have evaluated the safety and efficacy of sildenafil in patients with diabetes, spinal cord injury, and depression.

Based on results of these and other controlled clinical trials, meta-analyses have recently been performed on treatment outcome with sildenafil as a function of age, severity of erectile dysfunction, and type of etiology. Age is not a significant predictor of treatment responsiveness. Patients over the age of 65 show approximately the same ratio of treatment efficacy compared to placebo as patients under the age of 65. Patients with mild ED displayed a slightly higher rate of improvement with sildenafil treatment than patients with moderate or severe ED. On the other hand, patients with mild or moderate ED also showed higher rates of response to placebo than patients with severe ED. If one takes into account the relative placebo response compared to active treatment in each



group, there is no evidence of improved treatment outcome as a function of disease severity. In other words, sildenafil is highly effective in older patients (> age 65) and in patients with more severe degrees of ED.

How effective is sildenafil in patients with different etiological conditions? Patients diagnosed with psychogenic ED show the highest rate of improvement with sildenafil treatment, compared to patients with mixed or purely organic etiologies. On the other hand, the placebo response rate was equally higher in the psychogenic and mixed groups, indicating an approximately equivalent rate of overall treatment responsiveness in each of the groups. The right side of Figure 4 shows the relative effectiveness of drug therapy compared to placebo in patients with diabetes mellitus (DM), spinal cord injury (SCI), and radical prostatecomy (RP). As shown, sildenafil treatment is least effective in patients with diabetes or following a radical prostatectomy. It should be noted, however, that placebo response rates are also very low (< 10%) in these two groups. Patients with spinal cord injury (SCI) show high rates of treatment responsiveness (> 75%) and the lowest rate of placebo response (< 5%), suggesting that sildenafil is especially beneficial in patients with SCI-induced erectile dysfunction. We are currently evaluating the effectiveness of sildenafil in women with spinal cord injury.

Sildenafil safety has been the topic of much controversy and debate in recent months. Based on adverse events reported in the main clinical trials, the drug has an acceptable overall safety profile. The most frequent adverse events reported were headache, flushing, dyspepsia, rhinitis, and visual disturbances. In the dose escalation and open label studies, these side effects were observed in less than 20% of patients and rarely resulted in drug discontinuation. Approximately 1-2% of patients withdrew from treatment due to drug side effects. Since the approval of sildenafil, increasing concerns have been raised regarding the potential cardiac risks associated with its use. In 1999, these risks were reviewed by a consensus panel of the American College of Cardiology (ACC),[10] which concluded that sildenafil poses no special cardiac risk for the large majority of patients. However, the drug is absolutely contraindicated for patients taking nitrates in any form, due to the likely potentiation of hypotensive effects with these drugs. Sildenafil should also be used with caution in patients with a recent history of myocardial infarction or other significant cardiac conditions (eg,

unstable angina, congestive heart failure). Caution is also recommended in patients using multiple antihypertensive agents.

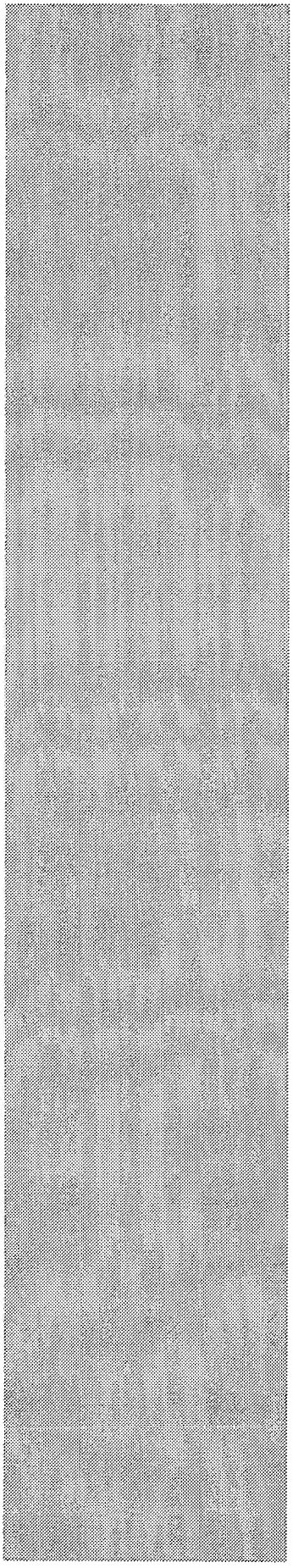
Other PDE-5 inhibitors are currently in development. These drugs may have greater selectivity or potency for the type-5 isoenzyme than sildenafil, although it is unclear at present whether such differences in **pharmacology** will have clinical significance. Clinical studies of sildenafil are also underway in women, although it is again unclear what role sildenafil will play in the future treatment of female **sexual** dysfunction.

At least one conclusion can be safely drawn at this time: sildenafil has had a major impact on the office management of male erectile dysfunction.[11] The availability of the drug has led millions of men to seek treatment for their condition who would not otherwise have sought professional help. In a related development, the treatment of ED has become largely the province of primary care practitioners, rather than urologists or mental health practitioners. The commercial success of sildenafil has also attracted the attention of the pharmaceutical industry at large, leading to investment of research funds in pharmacologic therapies for other **sexual** disorders in men and women. The long-term results of this investment will undoubtedly have a major impact on medicine and society in the years to come.

Dopamine Agonists

Penile erection is initiated by specific structures and neural networks in the central nervous system. Supraspinal sites that project directly to the spinal cord center for penile erection include the paraventricular nucleus (PVN), the locus caeruleus (LC), nucleus paragigantocellularis (NPGi), and the medial preoptic area (MPOA) of the hypothalamus. Dopamine is a monoaminergic neurotransmitter that has localized activity in the PVN and MPOA of the hypothalamus. It is excitatory to oxytocinergic pathways that project to the spinal erection generator. Currently, only one centrally active agent, sublingual apomorphine, is in advanced development for the treatment of ED.

Apomorphine is a dopamine agonist that is active in both D1 and D2 receptors, although it is slightly more selective for the D2 compared to the D1 receptor. Apomorphine is not an opiate, but rather an aporphine that in rats produces erections in **sexual** situations. It is a well-known agent



that has been available medically since 1869. However, a novel sublingual formulation has been recently developed that appears to be both effective and safe.[12] Overall, it has demonstrated up to 60% efficacy in producing "erections adequate for intercourse" in doses ranging between 2 mg and 6 mg. The major side effects are nausea, which occurs in up to 20% of patients at the higher doses, and syncope, which occurs in less than 5% of patients at higher doses. Few if any patients experience syncope at the 2 mg or 4 mg doses. The availability of centrally active erectogenic agents raises new questions and opportunities for both researchers and clinicians. Sublingual apomorphine is currently in advanced stages of clinical testing and is likely to be the second orally active agent approved for the treatment of erectile dysfunction. It has been suggested that due to the central actions of this drug, it may have particular relevance in the treatment of **sexual** dysfunction in women.

Alpha-1/Alpha-2 Blockers

The availability of sidenafil has focused attention on the nitric oxide "excitatory" pathway for initiating corporal smooth muscle relaxation and penile erection. Of equal potential importance is the "inhibitory" contractile pathway that controls corporal smooth muscle contraction and penile detumescence. A complete conceptualization of the mechanisms of penile erection involves both contractile and relaxatory pathways. Detumescence of the erect penis occurs via adrenergic stimulation, which induces: (1) contraction of the cavernosal arteries leading to reduced arterial inflow, and (2) contraction of the trabecular smooth muscle, which causes collapse of the lacunar spaces. Detumescence of the erect penis is mediated primarily by adrenergic nerve terminals releasing norepinephrine to alpha-1 and alpha-2 adrenergic receptors on the corporal smooth muscle cell and cavernosal artery. Conversely, local alpha-adrenergic blockers, such as phentolamine mesylate or doxazosin, have been shown in both in vivo and in vitro studies to prevent detumescence, to prolong the duration of erection, and to potentiate the stimulatory effect of smooth muscle relaxation by removing inhibitory responses mediated by the sympathetic nervous system.

Phentolamine mesylate is a combined alpha-1 and alpha-2 adrenergic antagonist that was originally approved for the treatment of pheochromocytoma-induced hypertension and norephinephrine-related dermal necrosis. Since the early 1980s, the drug has been used in combination with

other agents for intracavernosal injection therapy of erectile dysfunction. Recently, a new oral, rapid-release formulation of phentolamine has been developed for treatment of mild or psychogenic erectile dysfunction.[13] Pharmacokinetic studies have shown the drug to be rapidly absorbed (Cmax = 0.25-0.75) and eliminated, and initial safety and efficacy has been demonstrated in several clinical trials.[14]

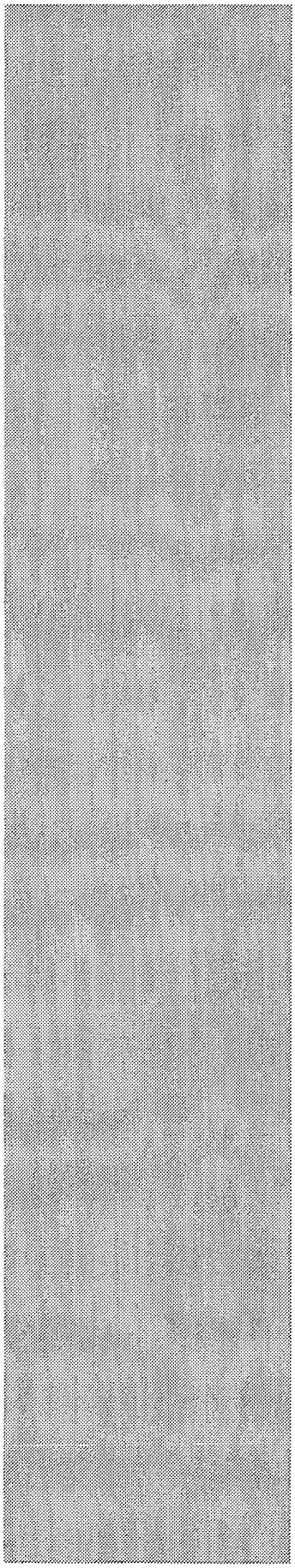
In a recent controlled trial, male patients with mild to moderate ED were randomized to receive oral phentolamine (40 mg or 80 mg) or double-blind placebo over a four-week treatment period. A dose-dependent effect of treatment was observed. Patients in the 80-mg group were approximately four times as satisfied with the results of treatment as patients in the placebo group, although fewer than 50% of patients overall reported satisfaction with treatment outcome. Results for the 40-mg group were intermediate. Phentolamine was well tolerated by most patients, with no serious side effects reported. Oral phentolamine has been approved for treatment of ED in relatively few countries (eg, Mexico, Brazil) at the time of writing. The drug is currently under review with the FDA.

Other ED Agents

A variety of other pharmacologic agents are currently in development for the treatment of ED. In particular, several companies have initiated research programs with other PDE-5 inhibitors that may offer potential advantages over sildenafil in terms of either selectivity or potency. It is uncertain, however, whether these pharmacologic differences will translate into clinical differences in safety or efficacy. In addition to the PDE-5s, other classes of agents are being investigated. For example, D2 selective dopamine agonists are under development, as are other adrenergic blocking agents. The safety or efficacy of these agents is unknown at present. Given the prevalence of ED in the population and the obvious commercial success of sildenafil, it is anticipated that clinical research in this area will increase markedly in the years to come.

Female Sexual Dysfunction

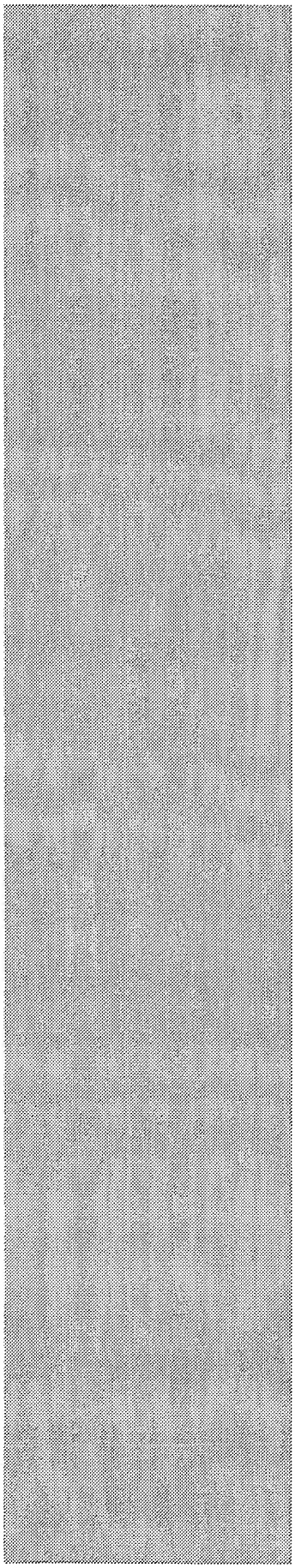
Female sexual arousal disorder (FSAD) is defined as "the persistent or recurrent inability to attain or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement."



Women with this disorder usually report little or no subjective experience of **sexual** arousal and may present for treatment with complaints of low **sexual** desire or anorgasmia. Although the true prevalence of FSAD is uncertain, epidemiologic studies have suggested that the disorder is common in women of all ages. Based upon data from the National Health and Social Life Survey, 19% of women aged 18-59 complain of recurrent lubrication difficulties.[15] Another recent study found that 14% of women complain of lack of lubrication during most or all **sexual** activity, while 23% have intermittent lubrication difficulties.[16] Among the postmenopausal women in this study, the incidence of persistent or recurrent lubrication problems increased to 44.2%. Similarly high rates of FSAD among postmenopausal women have been reported. Despite the prevalence of this disorder, few pharmacologic approaches to treatment have been investigated to date.

In an initial pilot study in our laboratory, we evaluated the effects of oral phentolamine on genital blood flow and subjective **sexual** arousal in a small sample of postmenopausal women.[17] The purpose of the study was to provide initial data on the safety and tolerability of the drug in women, and to evaluate the effects of oral phentolamine on physiological and subjective measures of arousal in response to visual **sexual** stimulation. Six postmenopausal women with a history of lack of lubrication or subjective arousal during **sexual** stimulation for at least six months were recruited for participation in the study. Subjects ranged in age from 48 to 62 years (mean = 54.5), and were an average of 4.8 years postmenopausal.

Vaginal photoplethysmography recording was used to assess changes in vaginal blood flow following drug administration. This method was first described by Sintchak and Geer, and has been widely used in laboratory studies of female **sexual** response. The vaginal photoplethysmograph consists of a light-emitting diode and sensitive photocell detector enclosed in a tampon-sized, clear acrylic probe. The signal obtained reflects changes in the amount of light back-scattered to the photocell from the surrounding vasculature, and provides a sensitive, albeit indirect measure of vaginal vasoengorgement. Depending upon the mode of recording, measures of vaginal blood volume (VBV) or vaginal pulse amplitude (VPA) can be obtained. VPA is regarded as the more sensitive and reliable measure, and



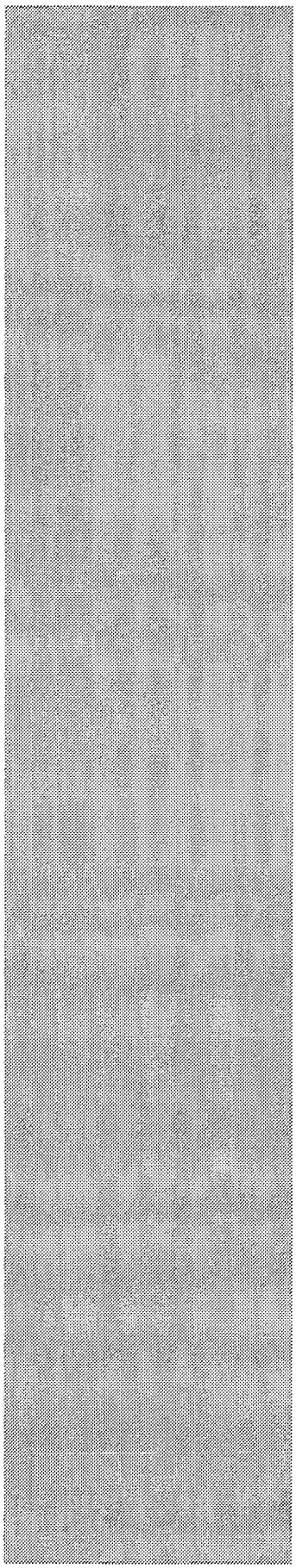
was accordingly selected for use in the present study. Visual **sexual** stimulation was provided by means of two 20-minute erotic videotapes showing conventional heterosexual activities. A 10-minute neutral videotape was shown prior to the erotic videotape to facilitate adaptation to the laboratory situation. A marked increase in responding occurred soon after onset of the erotic stimulation. On the self-report measures of **sexual** arousal, two of the scales (self-reported lubrication, tingling sensations) showed a significant difference between drug and placebo conditions ($P < .05$), and a third scale (subjective pleasure) approached statistical significance ($P < .10$). Additionally, few adverse drug reactions were noted during the course of the study, and the drug was well tolerated overall. These results await replication in a large-scale, controlled clinical trial.

Several uncontrolled trials have been reported on the use of sildenafil in women with arousal disorders of various types. These results have been equivocal to date, and clearly warrant further investigation in well-controlled trials. In addition to vasoactive agents, several studies have evaluated the effects of androgenic agents in the treatment of hypoactive **sexual** desire disorder and other **sexual** difficulties in women. The principal findings from this research are presented in a recently published article in this journal.[5]

Premature Ejaculation

Premature ejaculation is a highly prevalent **sexual** disorder that affects up to 30% of men of all ages.[15] Although it is a more common disorder in community samples than ED, a smaller number of patients with premature ejaculation present for treatment. Various pharmacologic approaches to treatment have been proposed, including most recently the use of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, and sertraline.[18] Clomipramine, in particular, has been shown to be a potent inhibitor of male ejaculation in several controlled studies. Although the drug is highly effective in controlling ejaculation, it is associated with significant anticholinergic side effects, such as dry mouth and somnolence. Other studies have shown clinically significant effects in association with paroxetine and sertraline. These latter agents are generally associated with fewer side effects and are better tolerated by most patients.

None of the studies reported to date have evaluated the



long-term effects of pharmacologic therapy of premature ejaculation.[18] It is uncertain whether the efficacy of treatment is maintained over time, or whether other sexual problems, such as erectile difficulties or hypoactive desire might be associated with these treatments. It is also uncertain whether pharmacologic treatments for premature ejaculation are superior to traditional behavioral treatments, or whether the two treatment approaches might be combined for superior efficacy. Despite these concerns, serotonergic agents are used with increasing frequency for the treatment of rapid ejaculation, and newer agents are in development that are more selective and potent. The long-term safety and efficacy of these new agents remains to be determined.

Conceptual and Methodological Issues

In reviewing the current research on pharmacologic treatment of sexual disorders in men and women, a number of conceptual and methodological issues need to be addressed. One of the key issues is the role of central and peripheral neurotransmitters in sexual response. Although several of the major neurotransmitters have been identified (e.g., NO, DA, NE), many others have yet to be investigated. Undoubtedly, the role of pharmacologic treatments will increase along with the growth of basic knowledge in neurotransmitter function. A number of key methodological issues need to be considered, such as the role of specific sexual effects of some drugs, compared to more indirect effects via mood change and other pathways. This is a particular concern when evaluating the sexual side effects of centrally active agents. Patient selection and placebo-blinding factors are important in all clinical trials in this area. The role of attributional and cognitive expectancy effects should always be considered, as patients frequently have strong expectations regarding the likely effects of certain pharmacologic agents on sexual behavior. Most clinical trials of ED show high placebo rates, generally in the 20% to 40% range. Finally, few studies have considered possible drug tolerance or potential dependency effects associated with pharmacologic agents for treatment of sexual dysfunction.

The long-term implications of pharmacologic treatments of sexual disorders warrant further consideration. Both positive and negative implications need to be considered. Among the positive implications of this trend are the likely improvements in treatment outcome, the potential

reduction in cost (compared to intensive psychological counseling or surgical intervention), and the likelihood of increased compliance and patient acceptance of treatment. Possible negative implications of pharmacologic treatments include the potential for abuse (ie, use in recreational or coercive situations) and potential long-term medical or psychological risks associated with drug treatments. It has also been suggested that the widespread use of these agents has contributed to the "medicalization" of **sexual** problems, along with other aspects of everyday life (eg, childbirth, menopause). These issues await further study and evaluation.

The author is a research consultant for Pfizer and for Zonagen, Inc.

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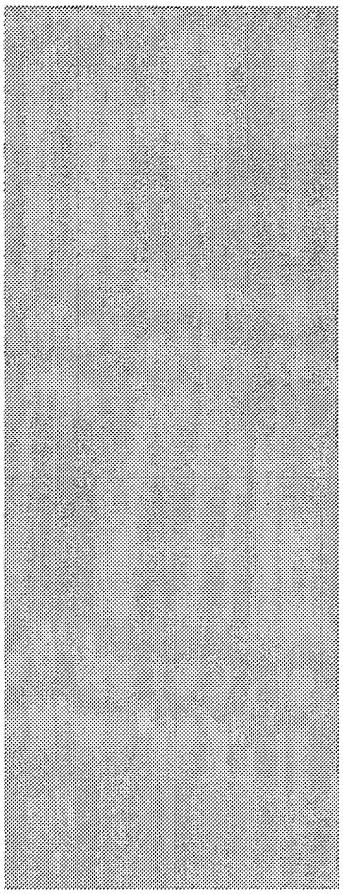

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The Human Sexuality WEB

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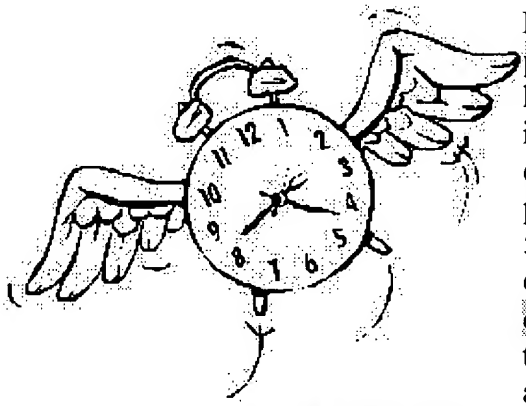
Early Ejaculation



Early **ejaculation**, or **premature ejaculation** as it was known in a less enlightened time, is a common male sexual dysfunction. Estimates of its prevalence range from 33% to 50% of all adult males experiencing a bout of early **ejaculation** at some point in their lives (usually at a younger age). Unfortunately, these high percentages make early **ejaculation** the most common male sexual dysfunction of all. But, fortunately for those who suffer with this problem, current treatments for early **ejaculation** are highly effective.

The question for most men then becomes, "how do I know if I'm ejaculating early or not?" Good question! Defining what constitutes early **ejaculation** has caused a great deal of debate amongst experts, primarily because any quantitative definition is inevitably subjective in nature. Several researchers have attempted to quantifiably define early **ejaculation** in the past, definitions which most often used either time limitations, or counted number of thrusts during vaginal containment of the penis. For example, attempts were made at defining early ejaculators as men who ejaculated thirty seconds to a minute after vaginal penetration; or men who ejaculated following five to ten thrusts after initial penetration. These quantifiable definitions are lacking in that they are not applicable to many men's situations. The most objective, and

therefore most useful, definition of early **ejaculation** remains that early **ejaculation** is when a man is consistently ejaculating sooner than he and his partner would prefer.

Any definition of early **ejaculation** must be qualified as to which of the two different types of early **ejaculation** are being experienced; **primary** or **secondary**. **Primary** early **ejaculation** refers to a man who has never had a sexual encounter were he was able to control his **ejaculation** for as long as he would like. **Secondary** early **ejaculation** refers to cases where the man was once able to control his ejaculations for a desired amount of time, but is no longer able to do so.

Early **ejaculation** is treated most effectively with a combination of couples counseling to deal with the emotional factors involved, and specialized cognitive-behavioral techniques such as sensate focus and the stop-start technique. Counseling for men who suffer with early **ejaculation** traditionally focuses upon issues related to performance anxiety, sex being seen as a penis-focused/goal oriented act, and issues surrounding masturbation. For example, approximately 90% of men report masturbating as an adult, and for many, masturbation was their first sexual experience resulting in orgasm. Male masturbation naturally tends to be a penis-focused act and there is usually a great focus on "finishing" as soon as possible for fear of being caught in the act. In other words, the goal of masturbation is orgasm, and the man tries to reach that goal as fast as he possibly can. As a result, many men learn to associate the entire sexual experience with the goal oriented, time limited act of masturbation. This example was not given to imply that all early **ejaculation** is the result of associations formed during childhood masturbation, or that all early ejaculators even masturbate; it was given as an example of issues which are likely to be dealt with in therapy for **treatment** of early **ejaculation**.

Research shows that if early **ejaculation** is treated by a professional sex therapist, with a dynamic approach to **treatment** as discussed above, there is a very good chance that both the male and his partner will be pleased with the results.

Links and References

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Impotency/Erectile Dysfunction

What is Erectile Dysfunction?

It is the inability of a man to achieve or maintain an erection sufficient for his sexual needs or the needs of his partner. Most men experience this inability at some point in their lives, usually by age 40, and are not psychologically affected by it. Some men experience chronic, complete erectile dysfunction (impotence), and others achieve partial or brief erections. Frequent erectile dysfunction can cause emotional and relationship problems, and often leads to diminished self-esteem. It has many causes, most of which are treatable, and is not an inevitable consequence of aging.

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What causes Erectile Dysfunction?

For years impotence was rarely mentioned or discussed. It was commonly believed to be due to psychological problems and **treatment** remained in the hands of the psychologists and psychiatrists. We know now that 80-90% of impotence is caused by physical problems, usually related to the blood supply of the penis.

There are three categories of causes

Psychogenic

Organic or physical

Neurological

Premature Ejaculation

Premature Ejaculation (PE) is the inability to maintain an erection long enough for mutual satisfaction.

Premature ejaculation is divided into a **primary** and a **secondary** form.

Primary Premature Ejaculation

Primary PE has been present since the patient first became sexually active. This patient has ALWAYS come too fast. The cause is often attributable to the element of haste in one's earliest sexual encounters.

This is learned behaviour, and like any learned behaviour it can be unlearned with the right help. This form of **primary** PE is psychogenic (as opposed to organic or physical) impotence.

Congenital Venous Leak

A subset of **primary** PE is those men born with congenital venous leak. The venous drainage system in the penis is not shutting down properly during arousal. The plug is loose in the drain in the bottom of the tub and the water runs out too fast. Many men in this group have never had a really hard erection. This is all fixable!

Secondary Premature Ejaculation

Secondary premature ejaculation means that after years of normal **ejaculation**, the duration of intercourse grows progressively shorter. Some men with severe PE will ejaculate during foreplay, even before penetration. This can be devastating. **Secondary** PE is due to physical causes, usually involving the penile arteries or veins or both.

Performance Anxiety

Another form of psychogenic impotence is performance anxiety. When you are stressed and anxious, erections may be difficult or impossible. Stress increases the body's production of catecholamines such as adrenaline and

nor-adrenaline, which are specific erection inhibitors. Learning to reduce your stress and anxiety levels under guidence will make it possible for you to produce long-lasting erections

Depression and Impotence

Depression is another cause of psychogenic impotence. Unfortunately, most anti-depressant medications themselves produce erectile failure, the last thing a depressed man needs.

Organic/Physical Impotence

By far, the most common cause of organic impotence, especially in older men, involves the penile arteries, the penile veins or both. When the problem is arterial, arteriosclerosis or hardening of the arteries is the usual culprit. Blunt trauma, sometimes from sports injuries, is a less frequent cause.

Impotence and Diabetes

Impotence is common in diabetics. Prolonged hyperglycaemia amongst many other processes also results in the thickening of capillaries, reducing blood and nutrient flow.

Lifestyle

The controllable risk factors for arteriosclerosis - overweight, lack of exercise, high cholesterol, cigarette smoking and high blood pressure - will produce erectile failure often before progressing to affect the heart. The coronary arteries (heart) are 1.5 - 2.0mm in diameter, the penile arteries are 0.6 - 0.7mm in diameter - 1/3 the size of the coronaries - and can become clogged sooner. Unless there is a change in lifestyle, coronary artery disease may follow impotence within a few years.

Neurologic Causes of Impotence

There are many neurological causes of impotence. Diabetes, as noted, chronic alcoholism, multiple sclerosis, heavy metal poisoning, spinal cord and nerve injuries, and nerve damage from pelvic operations such as prostatectomy can produce erectile dysfunction.

Drug-Induced Impotence

A great variety of prescription drugs such as blood pressure

medications, anti-anxiety and anti-depressant drugs, glaucoma eye drops, and cancer chemotherapy agents are some of the many drugs associated with impotence.

Hormone-Induced Impotence

Hormonal abnormalities such as increased prolactin (a hormone produced by the anterior pituitary gland), steroid abuse by body-builders, too much or too little thyroid hormone and hormones administered for prostate cancer may cause impotence. Rarely is low testosterone alone responsible for poor erections.

Sometimes congenital or acquired anatomic abnormalities prevent erections, such as Peyronie's Disease, an acquired curvature of the penis.

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How are the causes diagnosed?

The diagnosis of erectile dysfunction does not involve embarrassing and invasive testing.
The diagnosis of erectile dysfunction involves techniques such as taking a medical and sexual history, asking about smoking, alcohol and medications. Only a standard physical examination is usually needed, including taking your blood pressure. Laboratory tests on blood and urine will help identify any underlying medical cause that may need **treatment**.

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Treatment for Impotence

A man experiencing erectile dysfunction should seek medical attention. He should locate a Urologist or physician that specializes in impotence diagnosis and **treatment**.

No one form of **treatment** is right for everyone. Your doctor or specialist will advise on your best cause of remedy

Nearly always there are several **treatment** options. These include lifestyle modification, short-term intensive counseling, self-administered injection , prescription drug modification, correction of hormonal imbalance, and penile prosthesis implants.

Here at Stenlake compounding we prepare a variety of tailor made options that your doctor may prescribe.

Apomorphine troches

Apomorphine/Phentolamine troches

Injections

Testosterone & DHEA Troches

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Sexual Medicine Program / Disorders of Ejaculation

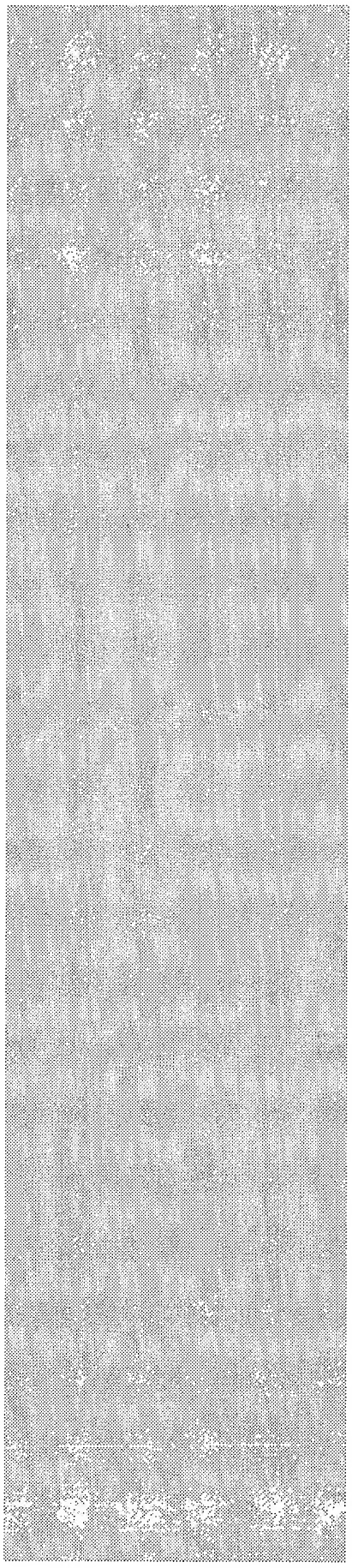
Disorders of Ejaculation

Ejaculation involves coordinated muscular and neurological even involve deposition of semen in the urine channel (emission) and e of the fluid from the urethral meatus (**ejaculation** proper). Emissio accomplished by contraction of the vas deferens, seminal vesicle ejaculatory ducts. This process is under adrenaline control. **Ejacu** proper results from the rhythmic contractions of the muscles arou urethra, which causes the forcible ejection of the ejaculate. Within spinal cord lies the [3]**ejaculation** center[2] which is the area involve coordination of signals from the brain and penis that eventually le **ejaculation**

There are 4 main ejaculatory disorders that are seen in clinical pr retrograde **ejaculation** (ii) **premature ejaculation** (iii) retarded **ejaculation** (orgasm) and, (iv) failure of **ejaculation** (anejaculatio

Retrograde ejaculation is the process whereby the semen is pas retrograde fashion into the bladder as opposed to out the urethra are 3 potential causes to this problem; anatomic (following bladde surgery or from a congenital process), neurologic (due to disorde interfere with the ability of the bladder neck to close during emiss as diabetes mellitus, retroperitoneal surgery) and pharmacologic paralysis of the bladder neck by certain medications). This proces diagnosed by the finding of seminal fluid and/or sperm within a ur specimen obtained immediately after orgasm.

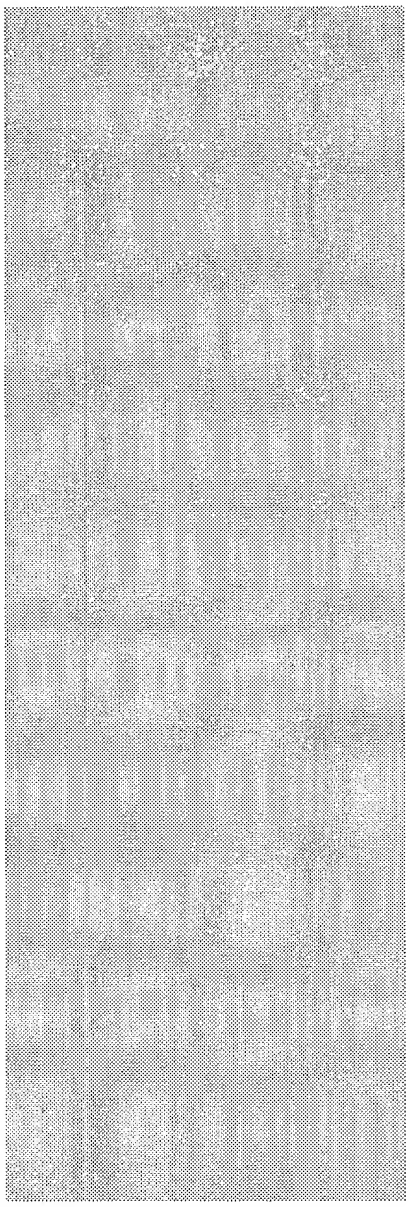
The **treatment** of retrograde **ejaculation** depends to some extent cause. Anatomic causes are rarely curable and sperm harvesting bladder is required for those patients wishing to initiate a pregnan



bladder is required for those patients wishing to initiate a pregnan Pharmacologic causes are generally reversible by withdrawal of t offending medication. Neurologic causes are difficult to treat if the complete nerve damage such as may occur in spinal cord injured In those patients with a partial neural injury (diabetes), the use of medications (pseudoepohedrine for example) may convert the pa an antegrade ejaculator.

Premature ejaculation, also known as rapid **ejaculation**, lacks a definition that is agreed upon by all practitioners but essentially is condition whereby a patient ejaculates with minimal sexual stimul before he wishes it to occur. It can be life-long (**primary**) or **seco** There are numerous theories as to the cause but most cases are multi-factorial with a contribution from both psychological and phy factors. This is believed to be the most common sexual dysfunctio males with almost 30% of men of all ages suffering from this cond Interestingly however, the quality of life of these patients is not ne affected by their condition. The management of this problem is be handled in a combined psycho-pharmacologic fashion. The use o medications to increase **ejaculation** time is useful in permitting th patients to practice senate focus exercises to recondition the ejac reflex. The latter technique is essential to the long-term cure of **pr ejaculation**. To date, there is minimal evidence-based data asses outcome of this therapeutic approach. At the **Sexual Medicine Pr** at **New York Presbyterian Hospital,** Dr. Mulhall works very close Dr. Michael Perelman, Co-Director of the **Human Sexuality Prog** the Department of Psychiatry in the management of patients with problem.

Retarded orgasm is a very difficult sexual dysfunction to treat. T condition involves the inability of the patient to achieve orgasm (**ejaculation**) in a timely manner and in severe cases men fail to a orgasm on any occasion. As men age, there is an increase in the takes to achieve **ejaculation**, however, in some men this increase lead to the inability to ejaculate within a 30 minute time period fro initiation of sexual stimulation. The causes of this condition includ use of certain anti-depressant medications (Prozac, Zoloft, Paxil, Celexa), sensory neurologic disorders affecting penile sensation occur with diabetic nerve damage), and psychological disorders (frequently seen in older men in their early experiences following d or being widowed). Finally there are men in whom there is no clea etiology for this problem and these are believed to have either a physiological or idiopathic form of this condition. There does not e pharmacologic strategy for these patients although there are anec reports of the use of the anti-depressant buproprion. If patients ar significantly bothered by this problem, as many of the sufferers ar use of penile vibratory therapy has the ability to permit patients to orgasm. The results are better in patients in whom there is a dela orgasm as opposed to those who have a consistent complete failu achieve orgasm.



Suggested Reading

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UPDATE! Learn more about testosterone replacement therapy.

by
Myron I. Murdock, M.D., FACS
Medical Director, HHH

Be the First: Learn About New Treatments on the Horizon for Treating Sexual Function

A new erectile dysfunction drug? Treatment for premature **ejaculation**? Safe, **effective** testosterone replacement therapy? YES! There are exciting new approaches on the horizon for treatment of these problems. The FDA has approved some of these new drugs, while others are beginning clinical field trials and being given patent approval. Here is a status report and you can discuss these with your care provider.

Testosterone Replacement Therapy

United Pharmaceuticals Incorporated (UniMed), a subsidiary of **Solvay Pharmaceuticals**, was recently approved by the Food and Drug Administration for the first topical gel for testosterone/androgen replacement. Approximately 4 to 5 million Americans and 2 percent to 16 percent of all erectile dysfunction patients have low levels of male hormones. Until recently injections every two to three weeks or daily patch therapy with a 33 percent irritation level have been the only

acceptable safe and **effective** therapies. Oral drugs are contraindicated for chronic use due to their liver toxicity.

The FDA has approved UniMed's **effective**, safe, convenient, nonirritating 1 percent testosterone gel, Androgel. This skin gel is only indicated in men with testosterone deficiencies with symptoms including erectile dysfunction, muscle weakness, osteoporosis, vasomotor instability including hot flashes, and depression due to androgen deficiency. Androgel is a clear, colorless gel that is applied once daily to the shoulders, upper arms, or abdomen, and dries within a few minutes. During that time the skin absorbs the testosterone and acts as a reservoir for the hormone which slowly enters the blood stream over the course of the next 24 hours. Normal male hormone levels are restored and symptoms are can be relieved.

The drug is not indicated for women, and pregnant women should certainly avoid contact that may cause significant harm to the fetus. Residual testosterone can be removed with soap and water. Testosterone should not be used to improve athletic performance. Patients interested in getting further information can do so online at www.unimed.com, or call toll free 1-877-463-7645.

Bayer's New Erectile Dysfunction Drug

Since Viagra™'s introduction the diagnosis and treatment of erectile dysfunction in men has been revolutionized. Viagra™ (*Sildenafil*) falls into a class of drugs called type V **phosphodiesterase** inhibitors. Type V is basically localized to the pelvic area whereas types I, II, III and IV are located in the eye, heart, blood supply, and gastroesophageal junction. The major side effects of Viagra™ include facial flushing, headaches, stomach upset, and a bright vision with a blue-green halo. All of these are the results of the nonspecific aspects of *Sildenafil*, i.e. it doesn't just affect type V, it affects type I, III and VI involving the eyes, the stomach, and the blood vessels.

Now Bayer Pharmaceuticals has just developed a new, more specific type V **phosphodiesterase** inhibitor called *Vardenafil*, which appears to be more potent than Viagra™ and a lower dosage may produce the same result. It has not been established yet whether it will work on patients that do not respond to Viagra™. Because it is more specific and involves, for all practical purposes, only type V inhibitors, this drug can have fewer side effects.

At this time there are major phase III clinical trials to determine *Vardenafil's* safety, dosage, and effectiveness. Over the next one to two years trial results will be completed.

An New Cream For Premature Ejaculation

Premature **ejaculation**, or the uncontrollable **ejaculation** immediately after vaginal penetration, causing dissatisfaction in the sexual life of both the man and his partner, probably represents a 20 to 30 percent

prevalence among men. Psychiatric counseling and behavioral therapy using the start-stop or squeeze techniques have been reported to be successful in 60 to 95 percent of the patients, but the remission rate is quite high. Patients with premature **ejaculation** have a heightened sensory response to stimulation in the genital region, and the inability to maintain a sympathetic dampening response as occurs in most men with an erect penis.

Medical therapies for premature **ejaculation** include topical anesthetics, serotonin re-uptake inhibitors (including Prozac, Zoloft, and Anafranil), sympathetic alpha blockade, and in extreme cases the use of injection therapy with Prostaglandin E-1 to maintain an erection beyond **ejaculation** for partner satisfaction.

These therapies are reported to be **effective** in 30 to 70 percent of the patients, but in some situations the side effects make then difficult to use. A new cream called SS Cream is a topical agent developed in Korea from the extract of nine natural products: Ginseng, Angelicae Gigantic Radix, Cistancis Herba, Zanthoxylli Fructs, Torlidis Semen, Asiasara Radix, Catyophylli Flos, Cinnamoni Cortex, and Bufonis Veneum. The cream appears to desensitize the penis and allows for longer, more satisfactory sexual performance.

In a recent study on 55 patients published in the **Journal of Urology**, approximately 80 percent had a positive effect, whereas fewer than 20 percent were affected by the placebo control cream. Mild, transient local side effects including penile warmth; burning and irritation occurred in fewer than 18 percent of the 530 trials in these patients. Interestingly, four of the patients reported delayed **ejaculation** of more than 45 minutes. SS Cream may soon be added to our armamentarium of already **effective** treatments for premature **ejaculation**.

Vivus Patent for Treatment of Premature Ejaculation

Vivus Incorporated recently announced that the U.S. Patent Office has awarded the company a patent for the administration of 5-HT.Sub.3 receptor antagonist to treat premature **ejaculation**. This patent provides Vivus with broad protection for the oral administration of this serotonin antagonist, specifically 5-HT3 agonist. The patent also allows administering this 5-HT3 agonist topically (as a cream), transdermally (with a skin patch), or transurethrally (directly through the penis).

In addition, Vivus has announced it will begin phase-2 studies in the United States and Europe with Alista trademark, of a proprietary topical formulation for the treatment of female sexual dysfunction. In December of 1999, Vivus filed a new drug application with the FDA for its second-generation erectile dysfunction drug Alibra, which is an intraurethral pellet containing Prostaglandin E-1 and the alpha I blocker Prazosin.